

REMARKS

Applicants filed an Amendment after Final Rejection on December 18, 2008, in the instant application. The Examiner issued an Advisory Action on January 23, 2009. Based on a telephone conversation with the Examiner on March 4, 2009, and statements in the Advisory Action, Applicants understand that the Examiner has entered the Amendment after Final Rejection and therefore claims 12-26 are pending (as amended on December 18, 2008) in the application.

Applicants further understand that the claim rejection under 35 U.S.C. §112, first paragraph, has been withdrawn. Therefore, the only outstanding issue in the application is the obviousness rejection under 35 U.S.C. §103.

Applicants thank the Examiner for the helpful telephone conversation on March 4, 2009.

I. Information Disclosure Statement

As a reminder, Applicants look forward to receiving a copy of the document list submitted with the Information Disclosure Statement filed on October 31, 2006, wherein receipt and consideration of the PCT publication listed near the top of the list is acknowledged.

II. Claim Rejections Under 35 U.S.C. §103

As noted in the Advisory Action, the rejection of claims 12-23 as being obvious under 35 U.S.C. §103 over Monte (US 2003/0147857) in view of Kruszewskya et al. (*Microecol. Therapy*, 2002), Kaur et al. (*Eur. J. Pharma. Sci.*, 2002) and Zhang et al. (*JBC*, 2002) has been maintained.

The Examiner has maintained the rejection of claims 12-23 on the basis that the combination of the four cited documents makes the subject matter of the pending claims obvious. Applicants respectfully continue to traverse the Examiner's position, both for the reasons of record and for the additional reasons set forth herein.

In order for the Examiner to maintain a rejection under 35 U.S.C. §103, the Examiner must show (i) that the claimed invention is merely the predictable use of known elements according to their established functions, and (ii) that there was an apparent reason to combine the known elements in the manner being claimed. *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Applicants contend that the Examiner has not established either element of the test set forth in *KSR*. Firstly, the Examiner has not established the claimed invention is merely the predictable use of known elements according to their established functions. In particular, the Examiner suggests that it would have been obvious to use some of the lactic acid bacteria disclosed in *Kruszewskya* in the method of Monte, in conjunction with the further teachings of Kaur and Zhang. However, as Applicants have previously pointed out, there is nothing in *Kruszewskya* to suggest that a formulation of four specific bacteria strains could be successfully used in the method of Monte, let alone used to produce the therapeutic effects recited in the pending claims. That is, there is no teaching or suggestion in any of the art cited by the Examiner that would suggest that the use of the claimed bacteria in a therapeutic method as claimed would have been a “predictable use” to the skilled artisan.

Applicants note that they have previously pointed out that a close reading of *Kruszewskya* reveals that it does not teach or suggest any beneficial properties stemming from the use of a formulation of all four of the recited strains. While *Kruszewskya* may disclose each of the four strains recited in the claims, it also teaches several other strains. Importantly, each of the strains disclosed in *Kruszewskya* was tested individually to determine its characteristics. (*Kruszewskya*, p. 43). *Kruszewskya* does not teach or suggest utilizing any of these strains in combination. Nor does *Kruszewskya* teach or suggest utilizing any of these strains in a formulation with at least one fiber. Thus *Kruszewskya* does not teach the predictable use of known elements. In the absence of experimental data there would have been no means to know *a priori* whether a

formulation comprising a combination of the four strains of Kruszewskya would have a therapeutic effect.

Indeed, Kruszewskya teaches away from the present invention. Kruszewskya recites that: “[t]here is also an increasing interest to add selected strains to food items to prevent or to treat various diseases, such as infections, allergy, inflammatory bowel disease and cancer.” However, Kruszewskya specifically concludes that “[o]ften the health claims on commercial products have been based on insufficient *in vitro* and *in vivo* data.” (Kruszewskya, p. 43). Kruszewskya further concludes that its own tests do not conclusively show that the strains tested therein are effective to treat any specific diseases. (Kruszewskya, p. 45). The inconclusive results of Kruszewskya do not teach the predictable use of known elements according to their established functions.

With regard to these arguments and others raised by Applicants in the Amendment filed December 18, 2008, the Examiner references particular characteristics of the selected LAB strains disclosed in Kruszewskya, such as acid and bile resistance, ability to colonize the human large intestine, GRAS status, use in the food industry (page 5 of the Advisory Action). The Examiner also notes that Kaur teaches probiotic formulations comprising multiple strains of probiotic bacteria for treating ulcerative colitis (stress-induced inflammation). The Examiner concludes that the skilled artisan could have been motivated to administer a combination of the four strains as taught by Kruszewskya and that the results would have been predictable. In support, the Examiner cites to the MPEP (without providing a citation) which is said to state that it is *prima facie* obvious to combine two compositions useful for the same purpose to produce a third composition having the same purpose.

Applicants appreciate the additional comments the Examiner has made regarding the teachings of Kruszewskya and Kaur, but again note that neither of these publications, nor Monte or Zhang, teaches or suggests that a formulation comprising the four specific bacterial strains recited in the claims would have the ability to treat a stress-induced inflammatory disorder in a mammal. As noted by the Examiner, the four publications

must be considered together. Monte appears to teach formulations comprising probiotics and prebiotics. Kruszewskya appears to teach the characteristics of seven different LAB strains. Kaur appears to teach, *inter alia*, a commercially available product comprising eight different bacterial strains that can be used in the treatment of ulcerative colitis. Zhang appears to teach that a particular enzyme (MPO) is a catalyst for lipid oxidation at sites of inflammation. None of these publications, alone or in combination, teaches or suggests that a formulation comprising the four specific bacterial strains recited in the claims would have activity in treating a stress-induced inflammatory disorder in a mammal.

Kruszewskya is the only publication that discloses characteristics of the four bacterial strains recited in the claims. However, as noted by the Examiner, these characteristics are limited to acid and bile resistance, ability to colonize the human large intestine, GRAS status, and use in the food industry. There is nothing in Kruszewskya to suggest that a formulation comprising the recited strains would have the recited activity. While a formulation comprising the strains might be expected to survive and colonize the human gut, Kruszewskya says nothing of the ability of a formulation of the four bacterial strains to treat a stress-induced inflammatory disorder. Similarly, while a formulation comprising the strains might have GRAS status and have been used in the food industry, again Kruszewskya says nothing of the ability of a formulation of the four bacterial strains to treat a stress-induced inflammatory disorder. As noted in Kaur, probiotic bacteria include at least three different genera and a large number of different species (pg. 1, right col.). As further noted by Kaur, probiotic bacteria are expected to have a “myriad” of beneficial effects (pg. 1, left col.), including the multitude of therapeutic effects noted at pages 2-7 of the publication. The Examiner has pointed to nothing in any of the cited documents that indicates all probiotic bacteria would be expected to have the ability to treat a stress-induced inflammatory disorder. The skilled artisan would not have had a realistic expectation *a priori* that a formulation having the four recited strains would have had such activity.

Indeed, as Applicants have already suggested, Kruszewskya discounts the idea that all probiotic bacteria would be expected to have the ability to treat a stress-induced inflammatory disorder. As Applicants have noted, Kruszewskya teaches that one of the bacterial strains in the claimed formulation (*Lactobacillus paracasei subsp. paracasei* F19) produces a pro-inflammatory cytokine (IL-8; see enclosed publication by Baggiolini et al. (*FEBS Letters* 307:97-101 (1992))), establishing IL-8 as a pro-inflammatory cytokine). This F19 bacteria would not have been expected to contribute in a positive manner to a formulation used to treat a stress-induced inflammatory disorder. Rather, it would have been a reasonable expectation that it would counteract the inflammation-reducing activity of the other bacteria in the formulation. In response to this point, the Examiner suggests at the bottom of page 6 of the Advisory Action that Kruszewskya teaches a mild immunostimulatory effect was exerted by the F19 bacteria and that IL-8 is a mediator of the innate immune system (the Examiner provides no evidence to support the latter contention). However, Applicants respectfully note that Kruszewskya does not provide any empirical data on this point. Further, there is nothing to suggest that the “mild” immunostimulatory activity of the F19 bacteria would counteract the effect of the pro-inflammatory cytokine produced by the bacteria.

Applicants also note a close reading of Kruszewskya suggests that the claimed formulation as a whole would not have the ability to treat a stress-induced inflammatory disorder. Kruszewskya states at page 42, col. 2, middle paragraph, that each of the bacteria in the claimed formulation activated NF- κ B. As discussed in the review by D’Acquisto et al. (*Mol. Interv.* 2:22-35 (2002)) being filed herewith, NF- κ B was known at the time of the Kruszewskya publication to be potent activator of pro-inflammatory genes (see, e.g., Abstract; paragraph bridging col. 1 and 2 on page 23). As such, a formulation comprising the four recited strains would not have been expected to have the ability to treat a stress-induced inflammatory disorder.

It is clear that given the disclosed characteristics of each of the bacterial strains recited in the claimed formulation (activation of NF- κ B, a known activator of pro-

inflammatory genes; production of the pro-inflammatory cytokine IL-8 by the F19 bacteria), the claimed invention is more than the predictable use of known elements according to their established functions. The skilled artisan would not have had a reasonable expectation that the claimed formulation could be used in the claimed method.

Applicants also incorporate herein their previous arguments that the skilled artisan would not have had an apparent reason to combine the known elements in the manner being claimed. As indicated above, due to the teachings of Kruszewskya regarding the pro-inflammatory characteristics of the recited strains, the skilled artisan would not have been motivated to combine them to produce the formulation recited in the pending claims.

While the Examiner cites to Kaur as supporting the combination of the teachings of Kruszewskya and Monte, as the Examiner has pointed out, Kaur teaches a probiotic preparation comprising eight strains for treating ulcerative colitis. The Examiner has pointed to no teaching or suggestion to support the idea that the eight strains of Kaur could be replaced by the four strains of Kruszewskya.

Moreover, as Applicants noted in the Amendment filed December 18, 2008, Kruszewskya is silent as to any possible anti-inflammatory activity of *L. mesenteroides* 23-77:1. Furthermore, there is no data supporting such an activity in Kruszewskya. Therefore the skilled person would not have been motivated to include this strain in the formulation of claim 12. The Examiner has responded to this point by noting at page 6 of the Advisory Action that the skilled artisan would have been motivated to include the 77:1 strain due to the additional ability of the strain to ferment fibers and act as a prebiotic. Applicants respectfully note that this point applies to all of the strains of the recited formulation (Kruszewskya, pg. 44, second col., second paragraph). Therefore, the skilled artisan would have had no reason whatsoever to include the 77:1 strain in the formulation as the other three strains have the noted abilities. Because inclusion of the 77:1 strain would lead to a more complex and more expensive formulation, the skilled artisan would not have been motivated by the reason provided by the Examiner.

Finally, the Examiner suggests at page 7 of the Advisory Action that the teachings of Kaur also support the inclusion of the F19 strain (*Lactobacillus paracasei* subsp. *paracasei* F19) in the claimed formulation. The Examiner states that the skilled artisan would have been motivated to use the immune stimulation exerted by F19 in order to provide resistance to pathogens. Applications again respectfully note that the claims are not directed to methods of increasing a host's resistance to pathogens through the administration of a probiotic formulation. Instead, the claims are directed to methods of treating a stress-inducing inflammatory disorder. Therefore, the skilled artisan would not have been motivated to include the F19 strain in the formulation on this basis.

In view of each of these points, the Examiner has failed to establish that the cited references teach or suggest the claimed method. Accordingly, in view of the forgoing differences, the claims are non-obvious and Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Conclusion

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

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